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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,355	06/23/1998	PETER J. KUSHNER	407J-896410US	2899

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EXAMINER	
PAK, MICHAEL D	

ART UNIT	PAPER NUMBER
1646	

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06/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/103,355	KUSHNER ET AL.	
	Examiner	Art Unit	
	Michael Pak	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

2. Applicant's arguments filed November 17, 2006, have been fully considered but they are not found persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 5 recite "first cell and the cell ...are the same cell" which is confusing because it is not clear how two separate cells in a method of previous claims can now be further limited in dependent claim to be a same cell.

4. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter and written description rejection.

Claim 16 encompasses a method with claim limitation of "transcription factor ligand is other than a compound having AP-1 mediated estrogenic activity..." which is not disclosed in the specification. However, the essential feature of the invention is a method that uses a transcription factor ligand which has AP-1 mediated estrogenic activity. The claims encompass a method which is not disclosed in the specification because the transcription factor ligands in the specification have AP-1 mediated estrogenic activity. No species are provided. *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification.

5. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method claimed wherein the transcription factor ligand has AP-1 mediated estrogenic activity, does not reasonably provide enablement for a method claimed wherein the transcription factor ligand is other than a compound having AP-1 mediated estrogenic activity. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of § 112 requires that the patent specification enable "those skilled in the art how to make and use the full scope of the claimed invention without `undue experimentation.'" Genentech, Inc. v. Novo Nordisk AIS, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)); see also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). ("[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Likewise, in Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), the court affirmed the holding of invalidity of claims to analogs of the EPO gene under § 112 for lack of enablement where applicants had

claimed every possible analog of the EPO gene but had disclosed only how to make EPO and a very few analogs. "[D]espite extensive statements in the specification concerning all analogs of the EPO gene that can be made, there is little enabling disclosure of the particular analogs and how to make them .... There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them." Id., 927 F.2d at 1213-14, 18 USPQ2d at 1027.

Claims encompass a method with claim limitation of "transcription factor ligand is other than a compound having AP-1 mediated estrogenic activity..." which is not disclosed in the specification. However, the specification discloses a method that uses a transcription factor ligand which has AP-1 mediated estrogenic activity. The claims encompass a method which is not disclosed in the specification because the transcription factor ligands in the specification have AP-1 mediated estrogenic activity. No species are provided with claimed functional activity in the method. The amount of direction provided in the specification is limited to a specific species a transcription factor ligand which has AP-1 mediated estrogenic activity. One skilled in the art would require empirical experimentation in order to determine the changes to method with a transcription factor ligand is other than a compound having AP-1 mediated estrogenic activity. Nuclear receptor ligands have AP-1 activity (Pfahl et al., US 6,004,748). Thus, one skilled in the art cannot use the method of transcription factor ligand is other than a compound having AP-1 mediated estrogenic activity. No working example is provided to determine whether a change in the method using a transcription factor

ligand is other than a compound having AP-1 mediated estrogenic activity. It would require empirical experimentation to determine a method using a transcription factor ligand is other than a compound having AP-1 mediated estrogenic activity. In view of the extent and the unpredictability of the experimentation required to practice the invention as claimed, one skilled in the art could not make the invention without undue experimentation. Therefore, based on the above Wands analysis, a preponderance of the evidence supports a conclusion that one skilled in the art would not have been enabled to make and use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1-7, 9-11, 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Pfahl et al. (US 6,004,748) with evidence by Kushner et al. (US 5,723,291).

Pfahl et al. teaches a method of detecting AP-1 interaction with cell containing estrogen receptors and as well as AP-1 promoter (columns 1-3 and 7-8). Columns 2 and 4 teaches the method using AP-1 proteins, cJun and cFos, by exogenous expression. Furthermore, column 2 teaches the method using AP-1 proteins endogenously expressing fos or jun. Column 2 teaches the method using the estrogen receptor as well as other nuclear receptors such as RAR, TR and GR. The pages 7-8 of the specification's definition of "AP-1 mediated estrogen activity" is generic to the teachings of Pfahl et al. and does not exclude the teachings of Pfahl et al. including effects of dexamethasone, thyroid hormone, retinoic acid or TPA. Kushner provide evidence that HeLa, CV-1, and NIH-3T3 cells inherently express estrogen receptor (column 12, Table I). The TPA interaction activates the AP-1 (column 3) which can be the transcription factor ligand for the protein kinase C which is the "cognate receptor" which is not excluded by the definition in the specification on page 6, lines 13-14. Glucocorticoid, thyroid hormone, retinoic acid or TPA are not excluded from the definition of a "transcription ligand factor" claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kushner et al.((AB); U.S. 5,723,291) in view of Pfahl et al.((A); U.S. 6,004,748), Evans et al.((B); U.S. 5,639,592), GAUB et al.((AV); Cell, 1990), Webb et al.(CB) and Kushner et al.((AD); WO 95/06754).

Kushner et al. teach a method with a cell or cells which express the estrogen receptors, Fos, jun, and AP-1 promoter fused to CAT gene (columns 2, 4-8, 10-12, and 17-20). The cells were contacted with estrogen which resulted in detection of the reporter CAT (column 10). Estrogen and antiestrogen have AP-1mediated estrogenic activity (columns 10 and 15-18). Furthermore, Kushner et al. teach a method using MDA453 cells (columns 5, 14 and 15) which express endogenous estrogen receptor by transfecting with estrogen receptor fusion protein (columns 13-15). The assays are performed with and without hormones (columns 13-15). Both fos and jun are in the methods of the assays in order for the AP-1 sites to work and thus are in contact with the cells. The cells are co-transfected with both estrogen receptor and Jun/Fos (column 13). The jun in the cell is c-jun (column 10). There are more than one cell in the assay. The negative control is taught by transfection with or without jun or fos at the same time or singly (columns 10 and 13). The estrogen receptor fusion protein or modified receptor is used in the transfected cells (column 6). Kushner et al. does not teach a cognate receptor which is not an estrogen receptor. Kushner et al does not teach contacting said first cell with said transcription factor ligand. Kushner et al. does not teach comparing expression of the reporter gene in the presence of the transcription factor ligand to expression of the reporter gene in the absence of the transcription factor

ligand wherein a difference in expression indicates that the transcription factor ligand modulates estrogen activation at an AP-1 site.

Evans et al. teach the method using a cell (such as HeLa, CV-1, NIH-3T3 cells; column 8) comprising c-jun, fos (column 5), and nuclear receptors (such as glucocorticoid, retinoic acid, estrogen, androgen, progesterone, vitamin D3, mineralcorticoid receptors; columns 6, 8-16). The column 7 teaches the method using AP-1 proteins by exogenous expression. Furthermore, column 5 teaches the method using AP-1 proteins endogenously or by administering fos or jun. Column 6 teaches the method using the estrogen receptor. The pages 7-8 of the specification's definition of "AP-1 mediated estrogen activity" is generic to the teachings of Evans et al. and does not exclude the teachings of Evans et al. Kushner provide evidence that HeLa, CV-1, and NIH-3T3 cells inherently express estrogen receptor (column 12, Table I).

Pfahl et al. teaches a method of detecting AP-1 interaction with cell containing estrogen receptors and as well as AP-1 promoter (columns 1-3 and 7-8). Columns 2 and 4 teaches the method using AP-1 proteins, cJun and cFos, by exogenous expression. Furthermore, column 2 teaches the method using AP-1 proteins endogenously expressing fos or jun. Column 2 teaches the method using the estrogen receptor as well as other nuclear receptors such as RAR, TR and GR. The pages 7-8 of the specification's definition of "AP-1 mediated estrogen activity" is generic to the teachings of Pfahl et al. and does not exclude the teachings of Pfahl et al. including effects of dexamethasone, thyroid hormone, retinoic acid or TPA. Kushner provide evidence that HeLa, CV-1, and NIH-3T3 cells inherently express estrogen receptor

(column 12, Table I). The TPA interaction activates the AP-1 (column 3) which can be the transcription factor ligand for the protein kinase C which is the "cognate receptor" which is not excluded by the definition in the specification on page 6, lines 13-14. Glucocorticoid, thyroid hormone, retinoic acid or TPA are not excluded from the definition of a "transcription ligand factor" claimed.

GAUB et al. teach a method using the cell comprising estrogen receptor, ovalbumin element which is target for transactivation by c-fos and c-jun linked to CAT reporter (page 1271 and figure 6). Cells are contacted with TPA or forskolin and the receptor (HE0) and fos and jun and reporter activity measured (page 1271 and figure 6). Page 6, lines 1-2, defines nuclear transcription ligand as a compound that binds to a nuclear transcription factor. TPA and forskolin activates the cell thus are compounds which have AP-1 mediated estrogenic activity. TPA are ligands for Protein Kinase C and forskolin is a ligand for adenylate cyclase. A second cell and figure 6 were performed with more than one cell in a cell culture which comprises the all the elements of the first cell . Limitation that the cells are the same which is met above. Claims 4 and 5 definition of "cognate receptor" in the specification on page 6, lines 13-14, does not further limit claim than the receptor in claims 2 and 3.

Webb et al.(CB) and Kushner et al.((AD); WO 95/06754) are cumulative reference with Kushner et al.((AB); U.S. 5,723,291) Pfahl et al.((A); U.S. 6,004,748), Evans et al.((B); U.S. 5,639,592), and GAUB et al.((AV); Cell, 1990).

It would have been obvious to modify the method of Kushner et al.((AB); U.S. 5,723,291) by incorporating the teaching of Pfahl et al.((A); U.S. 6,004,748), Evans et

al.((B); U.S. 5,639,592), and GAUB et al.((AV); Cell, 1990) and further use the glucocorticoid receptor, retinoic acid receptor, or other nuclear receptors as cognate receptors which are not estrogen receptor. Having created the method above, it would have been obvious to modify the method to add the transcriptional ligand and comparing it to control. One of skilled in the art would have been motivated combine the teaching of the references because they are analogous references which teach nuclear receptors interaction with AP-1 site and AP-1 protein interaction. Further motivation is provided by Evans et al. who teach that understanding the mechanism of the regulatory effect of hormones, receptors, and AP-1 transcription factors are important to determine undesirable side effects especially as it relates to proto-oncogenic effects of cell growth and differentiation (columns 1 and 2). Evans et al. motivation is especially important in view of the regulatory interaction of estrogen signalling pathway with glucocorticoid, progestins, and androgens as taught by Gaub et al. (Pages 1267 and 1273). Further motivation is provided by Pfahl et al. who teach that methods of the invention can be used to identify and screen new ligand of nuclear receptor useful for treatment of cancer because the receptors (such as estrogen and glucocorticoid etc.) interaction with AP-1 (columns 1-3). One skilled in the art would have been motivated to add the ligand because the testing of the method requires activation of the cognate receptor. One skilled in the art would have been motivated to compare the ligand effect to control because the testing of the method requires comparison of the activation of the cognate receptor with a control which is a standard laboratory technique.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,723,291 in view of Pfahl et al.((A); U.S. 6,004,748), Evans et al.((B); U.S. 5,639,592), GAUB et al.((AV); Cell, 1990), Webb et al.(CB) and Kushner et al.((AD); WO 95/06754). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The reason for the rejection has been set forth in the previous office action.

The teachings of Pfahl et al.((A); U.S. 6,004,748), Evans et al.((B); U.S. 5,639,592), GAUB et al.((AV); Cell, 1990), Webb et al.(CB) and Kushner et al.((AD); WO 95/06754) are discussed above.

Cognate receptors which are not estrogen receptor are not taught by Kushner et al.((AB); U.S. 5,723,291). Kushner et al does not teach contacting said first cell with said transcription factor ligand. Kushner et al. does not teach comparing expression of the reporter gene in the presence of the transcription factor ligand to expression of the reporter gene in the absence of the transcription factor ligand wherein a difference in expression indicates that the transcription factor ligand modulates estrogen activation at an AP-1 site.

It would have been obvious at the time of the invention to modify the method of claims 1-27 of U.S. Patent No. 5,723,291 by incorporating the teaching of Pfahl et al.((A); U.S. 6,004,748), Evans et al.((B); U.S. 5,639,592), and GAUB et al.((AV); Cell, 1990) and further use the glucocorticoid receptor, retinoic acid receptor, or other nuclear receptors. Having created the method above, it would have been obvious to modify the method to add the transcriptional ligand and comparing it to control. One of skilled in the art would have been motivated combine the teaching of the references because they are analogous references which teach nuclear receptors interaction with AP-1 site and AP-1 protein interaction with interests in understanding cancer cell growth regulation. Further motivation is provided by Evans et al. who teach that understanding the mechanism of the regulatory effect of hormones, receptors, and AP-1 transcription factors are important to determine undesirable side effects especially as it relates to

proto-oncogenic effects of cell growth and differentiation (columns 1 and 2). Evans et al. motivation is especially important in view of the regulatory interaction of estrogen signalling pathway with glucocorticoid, progestins, and androgens as taught by Gaub et al. (Pages 1267 and 1273). Further motivation is provided by Pfahl et al. who teach that methods of the invention can be used to identify and screen new ligand of nuclear receptor useful for treatment of cancer because the receptors (such as estrogen and glucocorticoid etc.) interaction with AP-1 (columns 1-3). One skilled in the art would have been motivated to add the ligand because the testing of the method requires activation of the cognate receptor. One skilled in the art would have been motivated to compare the ligand effect to control because the testing of the method requires comparison of the activation of the cognate receptor with a control which is a standard laboratory technique.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Pak whose telephone number is 571-272-0879. The examiner can normally be reached on 8:00 - 2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-083535. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Michael D. Pak

Michael Pak
Primary Examiner
Art Unit 1646
13 June 2007